

Existing trends and applications of artificial intelligence in urothelial cancer

A scoping review

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INTRODUCTION

The use of artificial intelligence (AI) in medicine is gaining significant traction. With the computational capability to mimic and perform human intellectual tasks, AI is being used to synthesize information, develop accurate diagnoses, and predict disease prognosis. Multiple reviews have detailed the use of AI in urology, including prostate cancer diagnosis, risk stratification and prognosis,^{1,2} predicting semen parameters for male fertility,³ stone composition in urolithiasis,⁴⁻⁶ and benign prostatic hyperplasia.⁴⁻⁶

Despite these efforts to summarize existing AI applications in various facets of urology, there has been no prior attempt to synthesize the literature on urothelial cancer (UC), including bladder cancer and upper tract urothelial carcinoma. Bladder cancer is the sixth most common cancer worldwide, with a five-year survival rate of 22% in late-stage cases.⁷ Although relatively uncommon, the incidence of aggressive upper tract urothelial carcinoma is also rising, resulting in an increased proportion of locally advanced and high-grade tumors.⁸ As such, a review of applications of AI in UC may greatly support clinicians.

This review aimed to summarize bibliometric, temporal trends, and prevailing themes among studies on AI applications in UC.

ABSTRACT

INTRODUCTION: The use of artificial intelligence (AI) in urology is gaining significant traction. While previous reviews of AI applications in urology exist, there have been few attempts to synthesize existing literature on urothelial cancer (UC).

METHODS: Comprehensive searches based on the concepts of “AI” and “urothelial cancer” were conducted in MEDLINE, EMBASE, Web of Science, and Scopus. Study selection and data abstraction were conducted by two independent reviewers. Two independent raters assessed study quality in a random sample of 25 studies with the prediction model risk of bias assessment tool (PROBAST) and the standardized reporting of machine learning applications in urology (STREAM-URO) framework.

RESULTS: From a database search of 4581 studies, 227 were included. By area of research, 33% focused on image analysis, 26% on genomics, 16% on radiomics, and 15% on clinicopathology. Thematic content analysis identified qualitative trends in AI models employed and variables for feature extraction. Only 19% of studies compared performance of AI models to non-AI methods. All selected studies demonstrated high risk of bias for analysis and overall concern with Cohen’s kappa (k)=0.68. Selected studies met 66% of STREAM-URO items, with k =0.76.

CONCLUSIONS: The use of AI in UC is a topic of increasing importance; however, there is a need for improved standardized reporting, as evidenced by the high risk of bias and low methodologic quality identified in the included studies.

METHODS

This scoping review was conducted on July 13, 2022, using the methodologies outlined by Arksey & O'Malley⁹ and Levac et al,¹⁰ and the protocol was prospectively registered on prospero (CRD42022326914). Search strategies were developed in collaboration with a librarian and reported following the preferred reporting items for systematic reviews and meta-analyses for scoping reviews (PRISMA-scr)¹¹ and JBI¹² guidelines. Relevant studies were identified a priori and used to validate the final search strategy.

Search strategy

Comprehensive searches based on the concepts of AI and UC were conducted using OVID MEDLINE (1946 to present), OVID EMBASE (1947 to present), Web of Science (1900 to present), Scopus (1990 to present), and the Cochrane Library (1998 to present). Grey literature was also searched to identify any non-indexed literature through searching open grey. A detailed search strategy for each database can be found in Appendix A (available at cuaj.ca).

Eligibility criteria

All studies that investigated the use of AI in UC were included. All forms of UC were considered, including urethral, bladder, and upper tract urothelial carcinoma. We considered any model that deviated from standard logistic regression (i.e., lasso, ridge, elastic net) as AI. Non-AI approaches include statistical methods, clinical judgment, or existing nomograms (e.g., EORTC or CUETO nomograms).

Studies were excluded if AI methods were not used or if non-UC neoplasms were described. Only studies written in the English language that reported any quantitative, qualitative, mixed- or multi-methods research, including both comparative (e.g., randomized, controlled, cohort, quasi-experimental) and non-comparative (e.g., survey, narrative, audit) methods were included. There were no restrictions on the date of publication. Reviews, abstracts, and conference proceedings were also excluded.

Data extraction and synthesis

Data abstraction was conducted by two independent reviewers and disagreements were resolved by a third reviewer. A standardized data extraction form was designed and piloted using a subset of studies prior to implementation. Data extraction included: disease state, area of research, sample size, AI model applications, AI models used, features for AI models, AI model perfor-

mance metrics, and comparison with non-AI models if available. Data analysis involved both a quantitative descriptive analysis and a qualitative theme-based analysis of AI applications in UC. Studies were reviewed and analyzed to identify major themes following inclusion.

Bibliometric data abstraction included date and country of publication, journal of publication, and journal impact factor at the time of publication. For feasibility purposes, a sample of 25 included studies were assessed for bias and quality of reporting. These 25 studies were chosen by randomly selecting five studies from each area of research (genomics, radiomics, clinicopathology, image analysis, and other) to ensure equal representation. This sample size accounts for 10% of all included studies and serves as a litmus test for future systematic review. Studies were assessed using the prediction model risk of bias assessment tool (PROBAST)¹³ and the STREAM-URO¹⁴ as an indicator of study quality. PROBAST is a standardized and validated tool designed to assess studies developing, validating, or updating prediction models across four domains, including study participants, predictors, outcomes, and analysis. Similarly, STREAM-URO is a standardized tool aimed at assessing complete reporting of diagnostic and prognostic machine learning studies in urology. Two reviewers independently assessed all 25 studies and conflicts were resolved by a third reviewer. Inter-rater reliability through Cohen's kappa statistic was measured for both PROBAST and STREAM-URO.

RESULTS

Search results

The initial database search yielded 4581 studies after duplicates were removed. From this, 474 studies underwent full-text review, and 247 of them were excluded for reasons listed in Figure 1. Ultimately, 227 studies were included for analysis.

Study characteristics

A detailed breakdown of study characteristics can be found in Table 1. Of the included studies, 47% explored UC diagnosis (n=107), 45% prognosis (n=102), and 7% both diagnosis and prognosis (n=18). The most commonly assessed disease state was bladder cancer without further subclassification (n=83), followed by muscle-invasive bladder cancer (n=40), and urothelial carcinoma (n=29). The included studies were categorized into major areas of research based on variables used for feature extraction; 33% focused on image analysis (n=74), 26% on genomics (n=56), 16% on

radiomics (n=36), and 15% on clinicopathology (n=35). Other, less common areas were grouped under “other,” which constituted 11% of studies (n=26). A summary of each included study based on area of research, including the UC disease states evaluated, the specific applications of AI used in their study, AI models used, features incorporated, available performance metrics, and whether their AI model was compared to non-AI models can be found in Appendices B–F (available at *cuaj.ca*). A list of our included studies can be found in Appendix G (available at *cuaj.ca*).

Bibliometric findings

The rate of publication of AI in UC studies has increased across all areas of research, as shown in Figure 2. Sixty-two percent of included studies (n=142) were published between 2019 and 2022 alone. Moreover, there has been an especially noticeable growth in the publication of studies in image analysis, genomics, and radiomics. The countries most involved in publishing studies on AI in UC include China (29%, 66/227), U.S. (24%, 55/227), and U.K. (8%, 18/227). Most of our included studies were published in healthcare-focused journals (53%, 120/227). Moreover, studies published in computer science or physics and engineering journals had a lower impact factor, on average, than studies in healthcare and basic science journals (Table 1).

Model characteristics

Only 57% of studies (n=129) attempted to validate the AI models developed. Of these, 35% (n=46) internally validated models, 33% (n=42) both internally and externally validated models with a single unique data set, and 32% (n=41) employed tuned models on additional data sets. All data sets for external validation were either publicly available or previously published in the literature. Features extracted for AI model development are found in Appendices B–F (available at *cuaj.ca*).

Comparison to non-AI models

Only 19% of studies compared the performance of their AI model to non-AI methods (n=42). Among these, 50% compared models to clinical judgment (n=21), 33% to traditional statistical methods (n=14), and 17% to non-AI nomograms or models (n=7). Overall, 90% of AI models (n=38) were found to significantly outperform conventional methods and clinical judgement. The remaining 10% (n=4) did not assess statistical significance between AI models and comparators.

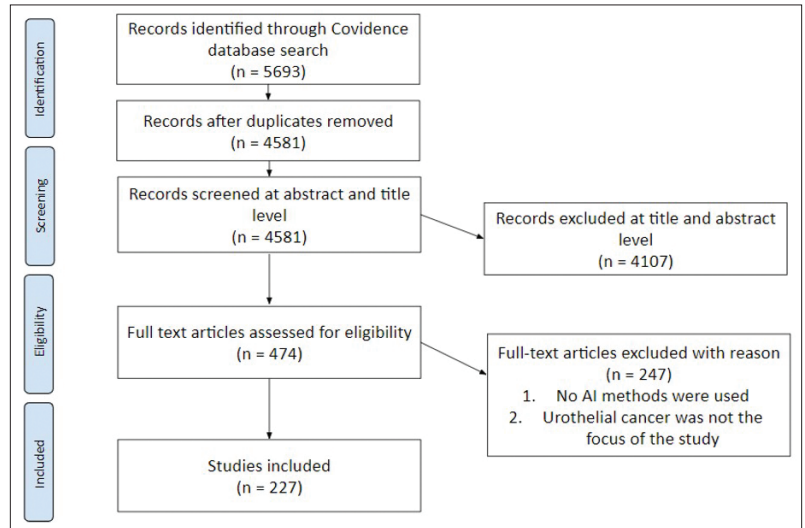


Figure 1. Preferred reporting items for systematic reviews and meta-analyses for scoping reviews (PRISMA-scr) flow diagram of the search process and study selection for the scoping review.

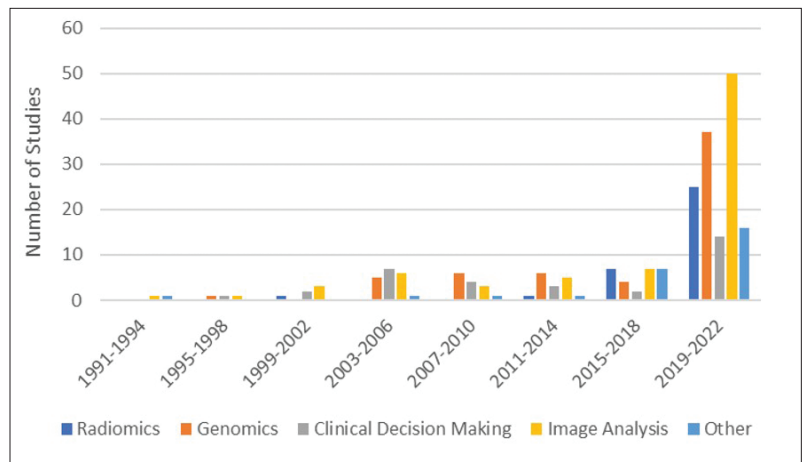


Figure 2. Temporal trend in publications and area of research of publications since 1991.

Risk of bias and methodologic quality assessments

Among 25 selected studies, 100% were marked as high risk of bias due to concerns of analysis, 96% due to participant data (n=24), 80% due to outcome data (n=20), and 64% due to predictors (n=16). Overall, all studies were deemed to be of high overall concern based on PROBAST (n=25). On average, 66% of STREAM-URO items were satisfied across the 25 studies. The criteria most commonly unmet were model specification (n=20), eligibility criteria (n=21), hyperparameter tuning (n=22), and bias assessment (n=24). Kappa scores of 0.68 and 0.76 were obtained for PROBAST and STREAM-URO assessments, respectively, indicating

substantial agreement between raters and high inter-rater reliability.

DISCUSSION

The use of AI in UC has been extensively documented in the literature. With growing interest in the field, AI is gaining attention as a tool for predicting various aspects of UC, including detection, staging, progression, and recurrence. Despite the significant number of AI models developed for UC, only a small fraction (19%) of the studies have compared their results to non-AI methods. This comparison is essential in determining the efficacy of AI models compared to traditional methods, which are less technically demanding and easier to design and implement.

AI applications in the included literature are pervasive, covering a broad spectrum of areas, including radiomics, imaging, genomics, and clinicopathology. The following sections provide an overview of the common trends in these key areas of research.

Radiomics

Radiomics is a field that involves extracting valuable information from medical imaging data to aid in clinical decision-making. In the context of UC, medical imaging plays a crucial role in diagnosis and prognosis. The majority of selected studies focus on computed tomography (CT) scans and magnetic resonance imaging (MRI), which are frequently used in bladder cancer patients. The studies selected for review were nearly equally split between those exploring AI use for UC diagnosis and those exploring AI use for prognosis ($n=15$). The studies also covered a broad range of clinical applications, including UC detection, staging, grading, segmentation, progression, treatment response, and survival.

Most radiomics studies have focused on classification tasks, such as determining the probability of disease or treatment response. Diagnostic studies have predominantly been concerned with determining TNM staging, while prognostic studies have focused on predicting progression-free survival. Support vector machines (SVMs) were most commonly used for these classification and regression tasks. The extracted features are aligned with the radiomics literature in other areas of oncology and typically combine demographic data with information about image signal intensity and spatial relationships between pixels. Lasso regression, a more interpretable model, was also often used in prognostic studies.

Image analysis

In the context of UC, AI image analysis has been applied in two main areas: images from endoscopic procedures, such as cystoscopy and ureteroscopy, and histopathologic images.

The use of AI in cystoscopic data focuses on detecting bladder cancer and staging tumors. AI-assisted cystoscopy has demonstrated high accuracy in image-based bladder cancer diagnosis and can detect subtle changes in the bladder wall. In addition, AI image analysis of cystoscopic images has been shown to improve tumor clearance during transurethral resection of the bladder.¹⁵ The studies involving ureteroscopic data primarily concern image segmentation of the lower and upper urinary tract, which is a branch of image processing that focuses on dividing the image into parts based on specific features and properties. This segmentation of different anatomical regions of the urinary tract supports further classification and prediction tasks, such as UC detection and prognosis. The selected studies involving AI image analysis with cystoscopy and ureteroscopy largely address classification tasks and use a diverse range of AI models, including multiple unsupervised techniques.

The selected studies on AI applications with histopathologic data primarily address UC prognosis. While urine cytology and identifying tumor characteristics are essential in bladder cancer diagnosis, the studies selected focus on predicting tumor response to treatment, progression, and survival. The histopathologic data is often used in conjunction with demographic information and imaging data from CT or MRI scans. There is a high degree of diversity among studies analyzing histopathologic data.

Genomics

Genomics-based studies aim to identify major genetic variants associated with UC, understand the molecular subtypes of UC, and determine which subtypes may benefit from specific chemotherapy regimens through pharmacogenomics.^{16,17}

The use of computational methods and AI to process genomic data has become increasingly important due to the growing complexity and volume of genetic data. Most genomic studies use gene expression profiles or DNA/RNA sequencing data as features for their AI models and focus on predicting UC prognosis, specifically the risk of disease progression, recurrence, or survival; however, the use of AI to predict treatment

Table 1. Summary of study characteristics for included studies

Study characteristics	n (%)
Number of studies	227
Disease states	
Bladder cancer (unspecified)	83 (36.6)
MIBC	40 (17.6)
NMIBC	20 (8.8)
Metastatic urothelial carcinoma	29 (12.8)
Metastatic bladder cancer	4 (1.8)
Upper tract urothelial carcinoma	1 (0.4)
Other	50 (22.0)
Outcomes of interest	
Diagnosis	108 (47.6)
Detection	60 (26.4)
Staging	33 (14.5)
Grading	26 (11.5)
Segmentation	19 (8.4)
Other	6 (2.6)
Prognosis	101 (44.5)
Survival	57 (25.1)
Recurrence	29 (12.8)
Treatment response	27 (11.9)
Progression	24 (10.6)
Other	4 (1.8)
Diagnosis & prognosis	16 (7.0)
Other	2 (0.9)
Areas of research	
Radiomics	36 (15.9)
Genomics	59 (26.0)
Clinicopathological	32 (14.1)
Image analysis	74 (32.6)
Other	26 (11.4)

IF: impact factor.

Table 1 (cont'd). Summary of study characteristics for included studies

Journal of publication	
Healthcare	120 (52.9), IF: 4.86
Physics & engineering	43 (18.9), IF: 2.86
Basic science	33 (14.5), IF: 5.16
Computer science	31 (13.7), IF: 3.36

IF: impact factor.

urine samples or urine sample biomarkers, with the potential for developing a non-invasive screening tool. Only a few studies aimed to identify novel genetic mutations associated with UC using unsupervised learning methods, such as neural networks and clustering algorithms to identify patterns from large sets of unlabeled genetic data.

Clinicopathology

Studies that use clinical or pathologic variables for predicting outcomes in UC focus on survival and disease recurrence, while very few investigate disease progression. The limited examination of treatment response prediction using clinical and pathologic data may be due to the limited characterization of UC subtypes.

The commonly used features in AI models for predicting UC outcomes are well-aligned, with established risk factors, including patient demographics, tumor characteristics, and laboratory values.^{18,19} Some studies attempt to expand the feature set by including less commonly associated variables. This is often done by comparing different combinations of features or by using an “all-in” approach. For example, Abuhelwa et al compared a curated list of 23 variables against an uncurated list of 75 variables to predict overall survival in muscle-invasive UC patients.²⁰

Artificial neural networks (ANNs) are the most commonly used AI models in clinicopathologic studies, with variations such as neuro-fuzzy models that incorporate fuzzy logic.^{21,22} These trained ANN models can be applied to new patient data to accurately predict UC outcomes, which has important implications for patient followup and prognostication post-treatment. For example, Jobczyk et al posit a novel, open-source ANN for the prediction of recurrence- and progression-free survival of non-muscle-invasive bladder cancer patients that outperforms the existing European organization for research and treatment of cancer, European Association of Urology and Club Urologico Espanol

response based on genetic information is still limited, given the limited characterization of gene expression profiles and molecular subtypes of UC.

Diagnostic studies of UC using genetic information have explored the detection of bladder cancer using

de Tratamiento Oncológico. Their data and code are publicly available.²³

Methodologic and reporting quality

While AI applications in the field of UC are becoming increasingly common, there are concerns about the quality of these studies. On average, the 25 analyzed studies only satisfied 66% of the STREAM-URO checklist, with especially low adherence to bias assessment, hyperparameter tuning, and eligibility criteria. Without bias assessment, subgroups that may preferentially benefit or be harmed without stratification based on relevant risk factors cannot be identified. Moreover, without disclosure of hyperparameter tuning or eligibility criteria, AI models published cannot be reproduced or assessed.

Similarly, all selected studies were deemed high risk of bias using PROBAST largely due to concerns of analysis and participant data. These studies failed to account for all participants and did not report attempts to optimize AI models. Without this information, it is difficult to assess whether features used for a given AI model correlate with any outcome(s) of interest. For example, Schuettfort et al was the highest in both reporting and methodologic quality, reporting no clinically meaningful predictive or prognostic value of systemic inflammatory response biomarkers in the selection of UC patients for perioperative systemic radiation.²⁴ As a result, researchers developing AI models in the field of UC are encouraged to follow the guidelines outlined in STREAM-URO and PROBAST to improve the transparency and quality of their studies.

Limitations

There are several limitations of our scoping review. A formal assessment of methodologic quality was only conducted on a sample of included studies, as the aim of the review was to provide a broad overview of trends in AI applications in UC literature. Additionally, the only performance metrics collected were accuracy, sensitivity, specificity, and area under the curve for the included AI models, as these were commonly reported and thus, best for comparison between different models. This may make it difficult to compare studies that report different performance metrics for their models. Moreover, potentially applicable studies from other languages may have been excluded from the current investigation, as this review included studies in English only. While additional limitations may stem from inconsistency and lack of coherence between themes, these were minimized by having multiple reviewers ensure concordance.

Future directions

Several AI applications in this review were found to significantly outperform nomograms and clinical judgment across areas of clinicopathology, image analysis, genomics, and radiomics; however, the lack of adherence to reporting tools, such as STREAM-URO and PROBAST, limits transparency and hinders the applicability of these models beyond their training data set. Efforts should be made to incorporate these reporting guidelines when developing AI studies in urology.

Moreover, the existing literature highlights a gap between AI model development and clinical implementation. No studies in this review validated their models compared to current standard of care in either a prospective or clinical trial setting. Future studies should look to methodologies to clinically integrate AI models, as outlined by Mccradden et al, to facilitate translation of these tools into clinical practice.²⁵

Lastly, most studies incorporated only one feature type (i.e., clinicopathologic, histologic, radiologic, or genomic data) for the diagnosis or prognostication of UC. A recent study by Esteva et al posits a multimodal AI tool that predicts long-term clinical outcomes using clinical and digital histopathologic features from prostate biopsy images.²⁶ Their tool (ARTERAAI) demonstrated superior performance across all oncologic endpoints compared to existing risk stratification tools and is now included in the latest National Cancer Center Network prostate cancer guideline.²⁷ This suggests that use of multimodal data in UC may better represent a patient's disease profile to improve predictive performance.

CONCLUSIONS

This scoping review provides an overview of the bibliometric trends and prevailing themes in the literature surrounding AI applications in UC. In recent years, publication of studies in AI applications in UC have increased rapidly. This is particularly true for studies in the areas of image analysis, genomics, and radiomics. Despite rapidly increasing interest, there remains a need for improved standardized reporting, as evidenced by the high risk of bias and low methodologic quality identified in a sample of our included studies using both PROBAST and STREAM-URO checklists. Additionally, this review compiles a catalog of studies on AI applications in UC. Further efforts to review this body of literature are recommended to continue to explore study quality and comparative success of AI models with non-AI methods.

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